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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Sprycel

dasatinib

Procedure no: EMEA/H/C/000709/P46/041

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 3 September 2015, the MAH submitted a completed paediatric study for Sprycel in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

SPRYCEL (dasatinib, Bristol-Myers Squibb [BMS]-354825) is a potent oral inhibitor of multiple oncogenic kinases and is approved for use in the European Union (EU), United States (US) and other countries for the treatment of adult subjects with chronic phase chronic myeloid leukemia (CML), advanced (accelerated and blast) phase CML, or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) who are resistant or intolerant to imatinib. Dasatinib has also been approved in the EU, US, and other countries for treatment of adult subjects with newly diagnosed chronic phase CML. The recommended starting dosage for chronic phase CML is 100 mg administered orally once daily (QD). The recommended starting dosage for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL is 140 mg QD.

This submission includes results for the pediatric study CA180204 (EudraCT number 2010 022946-25) and is being submitted in accordance with Article 46 of Regulation (EC) No. 1901/2006. A final clinical study report (CSR) is included in the submission and presents subject disposition, exposure, safety, and efficacy data. Study CA180204 started in 15-Jul-2008 and completed on 05-Mar-2015.

CA180204 is a completed, open-label, multi-center, single-arm Phase 2 study conducted and sponsored by the Children's Oncology Group (COG, AALL0622) assessing the addition of dasatinib administered QD to a multi agent chemotherapeutic "backbone" in children with newly diagnosed Ph+ AL). This study builds on the experience of COG AALL0031, which incorporated imatinib, a tyrosine kinase inhibitor (TKI) targeting BCR-ABL, into an intensive chemotherapy backbone for the same population. Compared with AALL0031, the treatment plan of CA180204 substituted dasatinib for imatinib, and eliminated radiotherapy for the great majority of children.

Preliminary data from this CA180204 trial prompted development of study CA180372, in which dasatinib is added to a Ph+ ALL chemotherapy regimen believed to be less intense than the AALL0031 chemotherapy backbone. The chemotherapy used in study CA180372 is based on the Associazione Italiana di Ematologia Pediatrica - Berlin-Frankfurt-Muenster ALL 2000 (AIEOP BFM 2000) study and amended European intergroup study on post-induction treatment of Philadelphia positive acute lymphoblastic leukemia (EsPhALL). Enrollment in study CA180204 was stopped on 3 Feb-2012 prior to reaching enrollment target when study CA180372 opened for enrollment of the same patient population in COG.

2.2. Information on the pharmaceutical formulation used in the study<ies>

The formulation used in the study was an oral tablet formulation. If necessary to permit administration in young children, the intact tablet could be placed, and allowed to dissolve, in 1 ounce of lemonade or preservative apple/orange juice.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study CA180204 a completed, open-label, multi-center, single-arm Phase 2 study conducted and sponsored by the Children's Oncology Group (COG, AALL0622) assessing the addition of dasatinib (Sprycel; BMS-354825) administered once daily (QD) to a multi-agent chemotherapeutic "backbone" in children from 1 years to less than 18 years of age (and adults) with newly-diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ AL)

2.3.2. Clinical study

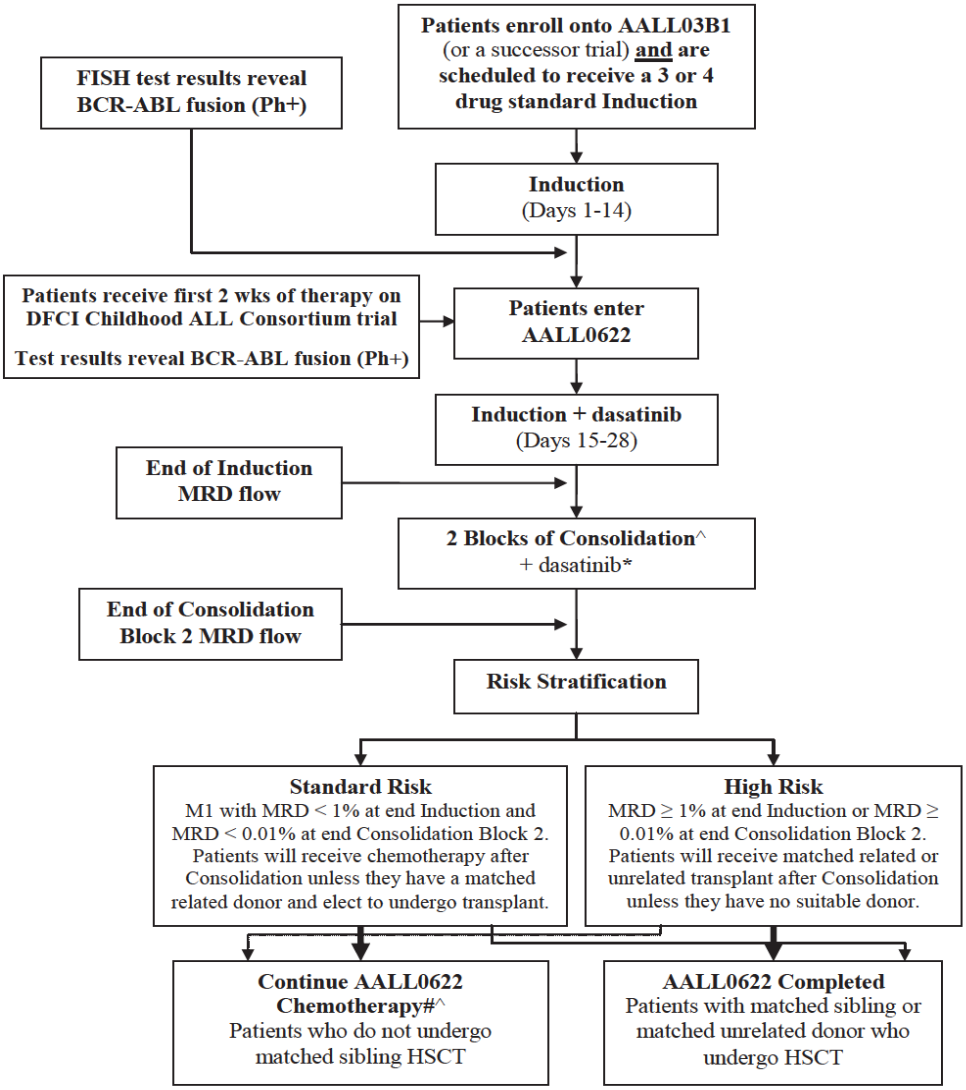
Description

Study CA180204 (COG AALL0622) is an open-label, multi-center, single-arm, Phase 2 study in children and young adults with newly diagnosed ALL. A primary objective of this study was to determine the feasibility and toxicity of an intensified chemotherapeutic regimen incorporating dasatinib for treatment of children and young adults with Ph+ ALL. Feasibility was defined as the ability to safely add dasatinib to the AALL0031 chemotherapy backbone either when given discontinuously (in 2-week periods followed by 1 to 2 weeks off) or continuously. An additional primary objective was to estimate the 3-year EFS for Standard-Risk Ph+ ALL subjects receiving dasatinib at the final chosen dose and intensive chemotherapy plus intensified TKI therapy. A benchmark EFS of 60% (the outcome of subjects receiving matched related bone marrow transplants from a large multicenter retrospective analysis), was used to evaluate outcome in this study.

A design schema is presented in Figure 1.1-1. Subjects entered CA180204 on or before Day 15 of Induction therapy (either a 3- or 4-drug standard Induction or on a Dana Farber Cancer Institute [DFCI] Childhood ALL Consortium trial) and received dasatinib on Days 15 - 28 of Induction. Following Induction, all subjects received 2 blocks of Consolidation. Subjects in Cohort 1 (Safety Phase) received dasatinib at 60 mg/m^2 daily (DL0) during the first 2 weeks of each 3- to 4-week post-Induction treatment block (discontinuous dasatinib). If this dose was well tolerated, the subjects in Cohort 2 received continuous dasatinib treatment at 60 mg/m^2/dose daily for the entire treatment block. (Note: If 60 mg/m^2 daily were not well tolerated, subjects in Cohort 2 would have received continuous dasatinib at 48 mg/m^2 daily [DL-1]). Subjects were enrolled into Cohort 2 once enrollment into Cohort 1 was stopped. Subjects in Cohort 1 (discontinuous dasatinib) received a total of 70 weeks of dasatinib. Subjects in Cohort 2 (continuous dasatinib) received a total of 128 weeks of dasatinib. See Figure 1.1-2 for schematic of safety phase.

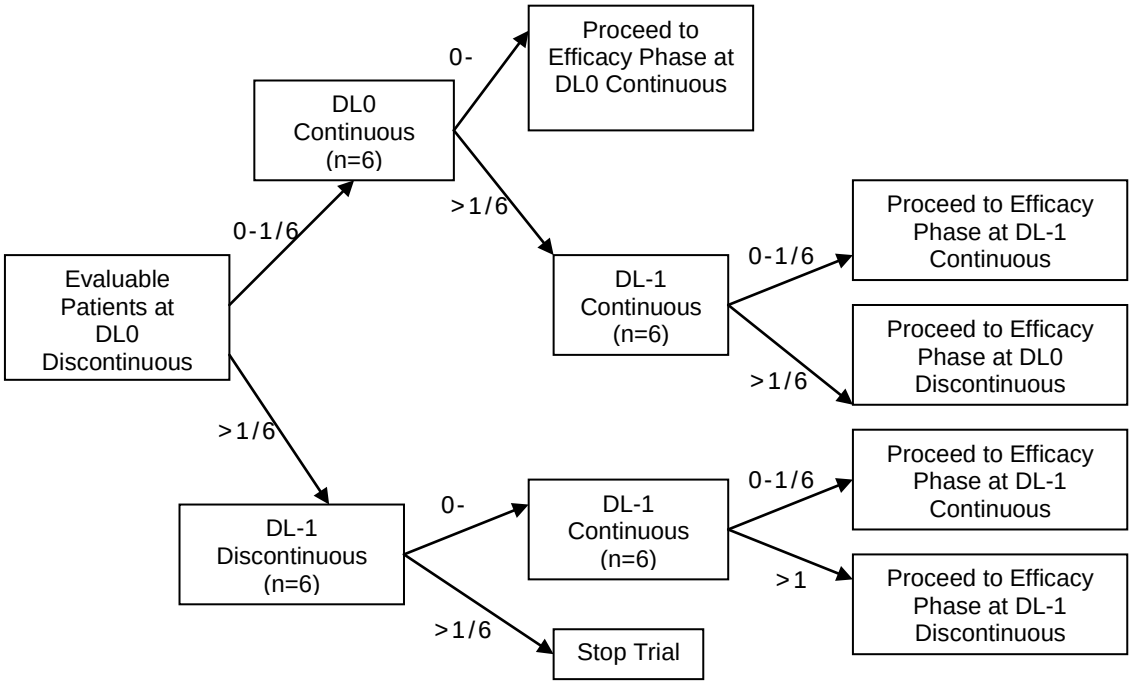
Quantification of residual disease at end of Induction and end of Consolidation was used to classify subjects into risk groups. All High-Risk subjects and all Standard-Risk subjects with matched sibling donors were urged to proceed to hematopoietic stem cell transplant (HSCT) at the end of Consolidation Block 2 on ASCT0431 or a successor COG transplant trial. All subjects who did not proceed to HSCT continued on CA180204 and received chemotherapy plus dasatinib.

Figure 1.1-1: CA180204 (AALL0622) Design Schema



*Dasatinib was given in first 14 days of each chemotherapy block for Cohort 1 and was given continuously during each chemotherapy block for Cohort 2.
#Remainder of CA180204 (AALL0622) chemotherapy followed AALL0031-Cohort 5 backbone chemotherapy, but with dasatinib substituted for imatinib. See Section 4.0 of the protocol for treatment details.
^Consolidation Block 1: Testicular irradiation for subjects with clinically evident or biopsy-proven testicular disease at end of Induction.

Figure 1.1-2: Diagram of Safety Phase



Note: Six subjects were evaluated beginning at DL0 (60 mg/m^2 daily), dose given discontinuously. If 2 or more of the 6 subjects had unacceptable delays, then the dose of dasatinib was reduced to 48 mg/m^2 daily (DL-1). An additional 6 subjects were then accrued at this lower dose level (DL-1). If ≥ 5/6 subjects safely completed Intensification Block 1 at a given dose level, Cohort 2 opened at DL0, with the dose given continuously. When a safe dose level was established, the efficacy phase of the trial opened to accrual. Subjects treated at the established dose level during the safety phase were included in the analyses for the efficacy phase.

Objectives

Primary objectives were:

- To determine the feasibility and toxicity of an intensified chemotherapeutic regimen that incorporates dasatinib for treatment of children, adolescents, and young adults (up to age 30) with Ph+ ALL.
- To determine whether the intensification of TKI through the addition of dasatinib in Induction (Days 15-28) and substitution of dasatinib for imatinib during post-Induction therapy, in the context of intensive cytotoxic therapy (according to AALL0031) and a good early response to therapy, will lead to a 3-year EFS of at least 60% in subjects with Ph+ ALL.

Secondary objectives were:

- To determine whether the addition of dasatinib during Induction therapy (Days 15-28) will decrease levels of MRD present at end of Induction therapy as compared with COG AALL0031.
- To determine whether early intensified TKI therapy (ie, addition of dasatinib on days 15 through 28 of Induction) will lower end-Consolidation MRD levels as compared to subjects on COG AALL0031 that received imatinib in Consolidation Blocks 1 and 2 (Cohorts 3-5).

- To determine the overall 3-year EFS rate for the whole cohort of Standard- and High-Risk subjects treated with dasatinib.
- To determine the long-term effects of dasatinib on growth and development and bone metabolism.
- To assess BCR-ABL mutation status at time of diagnosis and progression/relapse.
- To assess overall survival (OS).

Criteria for Evaluation

Safety primary endpoint: A primary objective of this study was to determine the feasibility and toxicity of an intensified chemotherapeutic regimen incorporating dasatinib for treatment of children and young adults with Ph+ ALL. Feasibility was defined as the ability to safely add dasatinib to the AALL0031 chemotherapy backbone either when given discontinuously (in 2-week periods followed by 1 to 2 weeks off) or continuously. Feasibility of administering dasatinib in combination with cytotoxic chemotherapy was assessed by examining 1) adverse event (AE) experience, 2) delays in administering the combination therapy (the occurrence of delays in each reporting period of greater than 14 days due to AEs was captured on case report forms), 3) impact on MRD levels at the end of Induction and end of Consolidation Block 2, and 4) effect on EFS.

Efficacy primary endpoint: An additional primary objective was to estimate the 3-year EFS for Standard-Risk Ph+ ALL subjects receiving dasatinib and intensive chemotherapy plus intensified TKI therapy. EFS was defined as the time from entry on study until an event. Events for EFS were defined as any first of the following: 1) induction failure, 2) relapse at any site, 3) secondary malignancy, and 4) death. A bone marrow aspirate was utilized in determining EFS. A bone marrow assessment was performed for cytology, conventional cytogenetics, and MRD assessment. A bone marrow aspirate was to be performed as clinically indicated if relapse was suspected in order to document an event for the primary endpoint of this study.

Statistical Considerations

Safety analyses were based on All Treated Subjects (all subjects who received at least 1 dose of dasatinib) and results are presented by cohort and across cohorts. The Efficacy Sample included all treated subjects with the exception of subjects considered ineligible based on study chair review, and the Pediatric Efficacy Sample included all treated pediatric subjects (< 18 years) with the exception of subjects considered ineligible based on Study Chair review.

The primary efficacy endpoint was 3-year EFS rate in Standard-Risk Ph+ ALL subjects in Cohort 2. The primary efficacy objective was to determine if in this group a 3-year EFS rate of 60% could be achieved. The rate of 3-year EFS was estimated from the Kaplan-Meier curve. A 1-sided 95% Wald confidence interval (CI) for 3-year EFS rate was constructed. A lower limit of the 1-sided 95% CI greater than 55% was evidence of this combination therapy being effective, but it should be taken into consideration that the sample size assumed in the protocol was higher than the actual sample size. The overall 3-year EFS rate for the combined groups of Standard- and High-Risk subjects in Cohort 2 was also estimated.

Secondary endpoints were 1) to determine whether the addition of dasatinib during Induction therapy (Days 15-28) decreases levels of MRD present at end of Induction therapy as compared with COG AALL0031, and 2) to determine whether early intensified TKI therapy (ie, addition of dasatinib on days 15 through 28 of Induction) lowers end-Consolidation MRD levels as compared with subjects on COG AALL0031 that received imatinib in Consolidation Blocks 1 and 2 (Cohorts 3-5). A total of 72 subjects on Cohorts 1-5 of study AALL0031 had end of Induction MRD data of which 71% were MRD positive (MRD > 0.01%). In addition, the MRD positive rate (at the 0.01% level) following Consolidation was

around 16%, in Cohorts 3-5 of AALL0031. A 1-sided, 2 sample Z-test of proportions was performed (alpha=5%) to compare the proportion of MRD positive subjects from Cohort 2 Efficacy Sample at end of Induction to that in study AALL0031, and a 1-sample Z-test of proportions (alpha=5%, 1-sided test) was used to compare the MRD positive rate among subjects in Cohort 2 with MRD data at end of Consolidation Block 2 to 16%.

Kaplan-Meier plots and estimates of OS were provided based on Standard-Risk Cohort 2 subjects as well as by cohort and across cohorts. BCR-ABL mutation status was analyzed at baseline and at disease progression or relapse for subjects that progress or relapse. Changes from baseline in height and weight z-scores (standardized based on World Health Organization selected pediatric parameters) at different time periods (baseline, year 1, year 2, year 3, and beyond year 3) were tabulated.

Results

Demographics and Baseline Disease Characteristics - All Treated Subjects

A total of 63 subjects were enrolled and 62 were treated (40 in Cohort 1 and 22 in Cohort 2). As indicated above, accrual was less than originally planned because enrollment was stopped when study CA180372 opened for enrollment of this patient population as agreed with regulatory authorities.

Overall, more male subjects were treated compared with female subjects (67.7% vs 32.3%, respectively), and the majority of subjects in this study were white (71.0%) (Table 1.2.1-1). The median age at time of informed consent in all treated subjects was 8.0 years (range 1 - 27 years) in Cohort 1 and 10.0 years (range 1 - 27 years) in Cohort 2. At the age of diagnosis, 3 subjects were > 1 - < 2 years, and 7 subjects were ≥ 18 years. The remaining 52 subjects were diagnosed between the ages of 2 and < 18 years.

The median time from initial diagnosis of ALL to the first dasatinib dosing date was 17 days overall (Table 1.2.1-2). The majority (93.5%) of subjects had B-precursor phenotype. The median white blood cell (WBC) and platelet counts, and the median % blasts in bone marrow at baseline were:

- WBC: 28.6 x 10^3/µL (range 2.0 - 700 x 10^3/µL)
- Platelet: 64.0 x 10^3/µL (range 5 - 45000* x 10^3/µL)
- Blasts in bone marrow: 88.0% (range 38% - 100%)

*Note: Post database lock, this single value of 45000 was assumed to be a data entry error. Removal of the value of 45000 leads to the following results for platelets:

- Cohort 1: N=39, Mean=90.9, Median=65, (Min, Max)=(5, 372), (Q1, Q3)=(29, 101), Standard Deviation=92.41
- Cohort 2: N=12, Mean=96.3, Median=51, (Min, Max)=(11, 254), (Q1, Q3)=(23, 176), Standard Deviation=87.05
- Total: N=51, Mean=92.2, Median=63, (Min, Max)=5, 372), (Q1, Q3)=(26, 134), Standard Deviation=90.35

Most subjects had central nervous system (CNS) 1 status (absence of blasts on cytospin preparation of cerebrospinal fluid), but 4 subjects (6.5%, 3 in Cohort 1 and 1 in Cohort 2) had CNS3 status at enrollment. No subjects were reported with testicular disease (or not applicable).

Table 1.2.1-1: Demographic Characteristics Summary - All Treated Subjects

	Cohort 1 N = 40	Cohort 2 N = 22	Total N = 62
AGE AT INFORMED CONSENT (YEARS)			
N	40	22	62
MEAN	9.9	10.3	10.1
MEDIAN	8.0	10.0	9.1
MIN, MAX	1 , 27	1 , 27	1 , 27
Q1, Q3	5.5, 14.6	5.3, 13.5	5.4, 13.9
STANDARD DEVIATION	6.20	6.08	6.11
AGE AT DIAGNOSIS (YEARS)			
N	40	22	62
MEAN	9.9	10.3	10.0
MEDIAN	8.0	9.9	9.1
MIN, MAX	1 , 27	1 , 27	1 , 27
Q1, Q3	5.4, 14.5	5.2, 13.5	5.4, 13.8
STANDARD DEVIATION	6.20	6.07	6.10
AGE AT DIAGNOSIS CATEGORIZATION (%)			
> 1 - < 2 YEARS	1 (2.5)	2 (9.1)	3 (4.8)
>=2 - < 7 YEARS	14 (35.0)	5 (22.7)	19 (30.6)
>=7 - < 12 YEARS	11 (27.5)	7 (31.8)	18 (29.0)
>=12 - < 18 YEARS	9 (22.5)	6 (27.3)	15 (24.2)
>=18	5 (12.5)	2 (9.1)	7 (11.3)
GENDER (%)			
MALE	26 (65.0)	16 (72.7)	42 (67.7)
FEMALE	14 (35.0)	6 (27.3)	20 (32.3)
RACE (%)			
WHITE	29 (72.5)	15 (68.2)	44 (71.0)
BLACK/AFRICAN AMERICAN	6 (15.0)	3 (13.6)	9 (14.5)
AMERICAN INDIAN/ALASKA NATIVE	1 (2.5)	1 (4.5)	2 (3.2)
ASIAN	1 (2.5)	2 (9.1)	3 (4.8)
NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER	1 (2.5)	0	1 (1.6)
OTHER	2 (5.0)	1 (4.5)	3 (4.8)
ETHNICITY (%)			
HISPANIC	7 (17.5)	3 (13.6)	10 (16.1)
NON-HISPANIC	30 (75.0)	15 (68.2)	45 (72.6)
EX-US	3 (7.5)	4 (18.2)	7 (11.3)
PERFORMANCE STATUS (ECOG) (%)			
1	26 (65.0)	13 (59.1)	39 (62.9)
2	8 (20.0)	9 (40.9)	17 (27.4)
3	6 (15.0)	0	6 (9.7)

Table 1.2.1-2: Baseline Disease Characteristics Summary - All Treated Subjects

	Cohort 1 N = 40	Cohort 2 N = 22	Total N = 62
TIME FROM DIAGNOSIS TO FIRST DASATINIB DOSING DAY (DAYS)			
N	40	22	62
MEDIAN	17.0	17.0	17.0
MIN, MAX	14 , 33	14 , 26	14 , 33
IMMUNOPHENOTYPE			
B-PRECURSOR	36 (90.0)	22 (100.0)	58 (93.5)
T-CELL	4 (10.0)	0	4 (6.5)
ACUTE LEUKEMIA, INDETERMINATE LINEAGE	0	0	0
PERIPHERAL WBC (10**3/UL)			
N	40	22	62
MEAN	95.3	87.3	92.4
MEDIAN	33.8	26.9	28.6
MIN, MAX	2 , 700	3 , 514	2 , 700
Q1, Q3	4.9, 133.6	9.8, 138.7	6.2, 138.7
STANDARD DEVIATION	146.64	126.77	138.91
PERIPHERAL BLAST COUNT (%)			
N	40	22	62
MEAN	40.8	48.8	43.7
MEDIAN	36.5	58.0	43.0
MIN, MAX	0 , 97	0 , 92	0 , 97
Q1, Q3	12.0, 76.0	19.0, 78.0	13.0, 77.0
STANDARD DEVIATION	33.43	33.58	33.43
HEMOGLOBIN (G/DL)			
N	40	12	52
MEAN	10.5	15.4	11.6
MEDIAN	8.7	8.6	8.7
MIN, MAX	3 , 76	4 , 93	3 , 93
Q1, Q3	7.2, 11.1	4.6, 12.7	6.7, 11.6
STANDARD DEVIATION	11.03	24.73	15.14
PERIPHERAL PLATELET COUNT (10**3/UL)			
N	40	12	52
MEAN	1213.7	96.3	955.8
MEDIAN	66.5	51.0	64.0
MIN, MAX	5 , 45000[a]	11 , 254	5 , 45000
Q1, Q3	29.5, 107.5	23.0, 176.0	27.5, 134.5
STANDARD DEVIATION	7101.33	87.05	6228.24
BONE MARROW EVALUATION			
YES	37 (92.5)	22 (100.0)	59 (95.2)
NO	3 (7.5)	0	3 (4.8)

BONE MARROW BLASTS (%)			
N	37	22	59
MEAN	86.6	84.1	85.7
MEDIAN	89.0	85.5	88.0
MIN, MAX	38 , 100	58 , 100	38 , 100
Q1, Q3	83.0, 95.0	79.0, 93.0	80.0, 95.0
STANDARD DEVIATION	12.12	11.64	11.91
NUMBER OF WBCS IN CSF			
N	40	20	60
MEAN	5.6	2.8	4.6
MEDIAN	1.0	1.0	1.0
MIN, MAX	0 , 158	0 , 34	0 , 158
Q1, Q3	0.0, 1.0	0.0, 1.0	0.0, 1.0
STANDARD DEVIATION	25.14	7.73	20.95
NUMBER OF RBCS IN CSF			
N	40	20	60
MEAN	35.5	1.5	24.1
MEDIAN	1.0	0.0	0.5
MIN, MAX	0 , 722	0 , 19	0 , 722
Q1, Q3	0.0, 2.5	0.0, 1.0	0.0, 2.0
STANDARD DEVIATION	136.17	4.24	111.91
BLAST PRESENT ON CYTOSPIN			
YES	7 (17.5)	4 (18.2)	11 (17.7)
NO	33 (82.5)	16 (72.7)	49 (79.0)
NOT REPORTED	0	2 (9.1)	2 (3.2)
CNS STATUS			
CNS1	33 (82.5)	16 (72.7)	49 (79.0)
CNS2	4 (10.0)	3 (13.6)	7 (11.3)
CNS3	3 (7.5)	1 (4.5)	4 (6.5)
NOT REPORTED	0	2 (9.1)	2 (3.2)

Note: Confirmation of Ph positivity occurred approximately 2 weeks from time of initial diagnosis.

[a] Post database lock, this single platelet value of 45000 was assumed to be a data entry error.

Efficacy results

In the protocol for CA180204, the expected number of Standard-Risk Ph+ ALL Cohort 2 subjects (ie, the group on which the primary efficacy analysis is based) was expected to be 73; however, due to early closure of the study in order to open the successor study CA180372, the actual number was 17. The sample sizes for efficacy analyses in Cohort 2 are considerably lower than expected per protocol due to the early termination of enrollment. This negatively affects the power of statistical tests and the precision of estimates; confidence intervals will be substantially wider than under the expected numbers of subjects. Therefore, inferences are also based on efficacy information from Cohort 1 (discontinuous dosing) even though exposure to dasatinib was considerably less.

No statistical comparisons were performed between Cohorts 1 and 2. These subgroups were not randomized; rather, Cohort 2 subjects were enrolled after it was concluded that toxicity levels were acceptable in Cohort 1 subjects and enrollment into that cohort was closed.

3-year Event-free Survival

Cohort 2 subjects: The primary efficacy endpoint was 3-year EFS rate in Standard-Risk Cohort 2 subjects. The proportion was estimated from the corresponding EFS Kaplan-Meier curve (Figure 5.1-1). The primary efficacy objective was to determine if in this group a 3-year EFS rate of 60% could be achieved. The protocol states further that if the lower limit of the CI would be greater than 55%, the combination therapy should be deemed effective. The estimated 3-year EFS rate was 70.1%. However, the lower limit of the 1-sided 95% CI was 51.8% (Table 5.1-1). At the 3-year timepoint, a total of 5 events had been reported, 1 subject had been censored, and 11 subjects remained at risk.

In Cohort 2 subjects (Any Risk, Efficacy Sample [secondary endpoint]), the estimated 3-year EFS rate was 66.3% (N = 21) with a lower limit of the 1-sided 95% of 49.4% (Table 5.1-1). At the 3-year timepoint, a total of 7 events had been reported, 1 subject had been censored, and 13 subjects remained at risk.

Overall for subjects in Cohort 2 (Any Risk, Efficacy Sample), one subject relapsed with ALL during study treatment (in CNS, after 21.7 months), and another subject developed secondary acute myelogenous leukemia (AML). Two additional subjects experienced relapse after completion of protocol

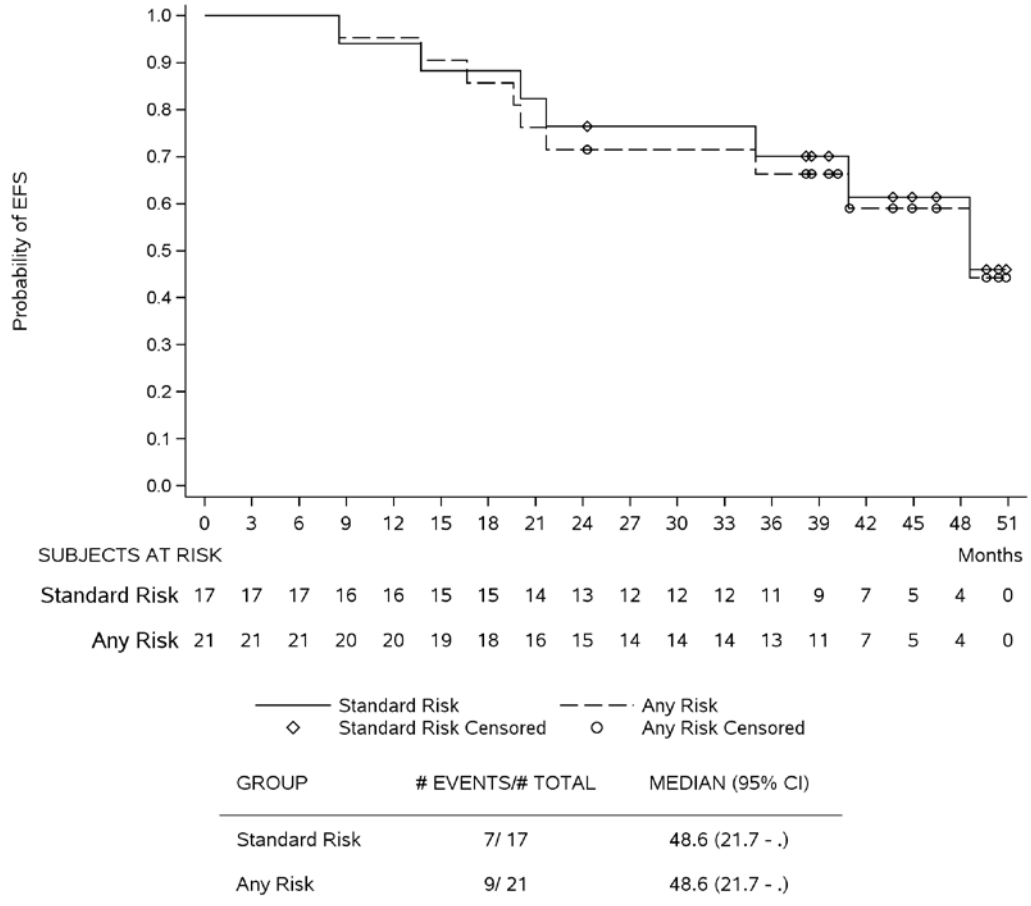
treatment. Of the 7 subjects who had been withdrawn for elective BMT, relapse was reported in 3 subjects and death related to graft-versus-host-disease (GVHD) in 1 subject.[Error! Bookmark not defined.]

Table 5.1-1: Proportions of Subjects in Cohort 2 with 3-Year EFS; Efficacy Sample

	Standard Risk N = 17	**High Risk N = 4**	**Any Risk N = 21**
Proportion (%)	**70.1**	50.0	66.3
95% 1-sided CI (%)	**51.8, 100**	8.9, 100	49.4, 100

Bold text is Primary Endpoint.
Source: CA180204 CSR[Error! Bookmark not defined.]

Figure 5.1-1: Kaplan-Meier Curves of EFS in Cohort 2 Subjects, Standard Risk and Any Risk - Efficacy Sample, Cohort 2



GROUP	# EVENTS/# TOTAL	MEDIAN (95% CI)
Standard Risk	7/ 17	48.6 (21.7 - .)
Any Risk	9/ 21	48.6 (21.7 - .)

Censored observations are represented by symbols.
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Program Name: rg-ef-km.sas 05AUG2015:00:54:53

In the Pediatric Efficacy Sample, the estimated 3-year EFS rate in Standard-Risk Cohort 2 subjects (N = 16) was 68.8% with a lower limit of the 1-sided 95% of 49.7%.[Error! Bookmark not defined.] At the 3-year timepoint, a total of 5 events had been reported, no subject had been censored, and 11 subjects remained at risk.

Combined Cohorts 1 and 2, Any Risk: The overall estimated 3-year EFS rate in combined Cohorts 1 and 2 (Efficacy Sample) treated with dasatinib was 79.6% with a lower limit of the 1-sided 95% CI of

70.9%.[Error! Bookmark not defined.] At the 3-year timepoint, a total of 12 events had been reported, 1 subject had been censored, and 46 subjects remained at risk. The 12 events reported at the 3-year time point included: Relapse or death after discontinuation from study for elective BMT (N = 6), relapse during study treatment (N = 2), relapse after completion of protocol treatment (N = 3), and secondary AML (N = 1).

In the Pediatric Efficacy Sample, the overall estimated 3-year EFS rate in combined Cohorts 1 and 2 (N = 52) was 80.8% with a lower limit of the 1-sided 95% CI of 71.8%.[Error! Bookmark not defined.] At the 3-year timepoint, a total of 10 events had been reported, no subject had been censored, and 42 subjects remained at risk.

Minimal Residual Disease

Cohort 2 subjects: Levels of MRD in Cohort 2 subjects (Any Risk) compared with COG AALL0031 at end of Induction therapy and at the end of Consolidation were assessed as secondary endpoints. At end of Induction therapy, 10/21 (47.6%) Cohort 2 subjects were reported with MRD < 0.01%.[Error! Bookmark not defined.] Although not statistically significant, a higher proportion of subjects in COG AALL0031 (51/72; 70.8%) compared with Cohort 2 subjects (N = 11/21; 52.4%) were MRD positive at end of Induction therapy (difference of -18.45%, CI -38.4, 1.5; p value = 0.0643). At end of Consolidation, 17/21 (81.0%) Cohort 2 subjects were reported with MRD < 0.01%. The proportion of MRD-positive Cohort 2 subjects (4/21; 19.0%) was not significantly different from historical data from subjects in COG AALL0031 (16.0%) (p-value = 0.3516).

In the Pediatric Efficacy Sample, 10/19 (52.6%) Cohort 2 subjects were reported with MRD < 0.01% at the end of Induction therapy.[Error! Bookmark not defined.] A statistically significant higher proportion of subjects in COG AALL0031 (51/72; 70.8%) compared with Cohort 2 subjects (N = 9/19; 47.4%) were MRD positive at end of Induction therapy (difference of -23.46%, CI -44.3, 2.7; p value = 0.0318). At end of Consolidation, 16/19 (84.2%) Cohort 2 subjects were reported with MRD < 0.01%. The proportion of MRD-positive Cohort 2 subjects (3/19; 15.8%) was not significantly different from historical data from subjects in COG AALL0031 (16.0%) (p-value = 0.4900).

Summary statistics for MRD at end of Induction and at end of Consolidation where MRD data are handled as semi-continuous and as categorized (< 0.01%, 0.01%-0.099%, and >= 0.1%) are presented for the Efficacy Sample and Pediatric Efficacy Sample in the CA180204 CSR.[Error! Bookmark not defined.]

Combined Cohorts 1 and 2, Any Risk: A lower proportion of subjects in combined Cohort 1 and Cohort 2 (N = 24/58; 41.4%) compared with subjects in COG AALL0031 (51/72; 70.8%) were MRD positive at end of Induction therapy (p value = < 0.0002).[Error! Bookmark not defined.] At end of Consolidation, 6/57 (10.5%) subjects in combined Cohort 1 and Cohort 2 were MRD positive compared with 16.0% from historical data in COG AALL0031 (p value = 0.1298).

In the Pediatric Efficacy Sample, a lower proportion of subjects in combined Cohort 1 and Cohort 2 (N = 20/51; 39.2%) compared with subjects in COG AALL0031 (51/72; 70.8%) were MRD positive at end of Induction therapy (p value = 0.0001).[Error! Bookmark not defined.] At end of Consolidation, 5/52 (9.6%) subjects were MRD-positive compared with 16.0% from historical data in COG AALL0031 (p-value = 0.1046).

Overall Survival

Cohort 2 subjects: The estimated OS rate at 3 years in Standard-Risk Cohort 2 subjects (Efficacy Sample) treated with dasatinib was 93.8% (95% CI: 82.3, 100).[Error! Bookmark not defined.] At the 3-year

timepoint, a total of 1 event had been reported, 1 subject had been censored (lost of follow-up), and 15 subjects remained at risk.

In the Pediatric Efficacy Sample, the estimated OS rate at 3 years in Standard-Risk Cohort 2 subjects (N = 16) was 93.8% (95% CI: 82.3, 100).[Error! Bookmark not defined.] At the 3-year timepoint, a total of 1 event had been reported, no subjects were censored, and 15 subjects remained at risk.

Combined Cohorts 1 and 2, Any Risk: The overall estimated OS rate at 3 years in combined Cohorts 1 and 2 (N = 59) was 93.2% (95% CI: 86.8, 99.6).[Error! Bookmark not defined.] At the 3-year timepoint, a total of 4 events had been reported, 1 subject had been censored, and 54 subjects remained at risk.

In the Pediatric Efficacy Sample, the estimated OS rate at 3 years in combined Cohorts 1 and 2 (N = 52) was 94.2% (95% CI: 88.0, 100).[Error! Bookmark not defined.] At the 3-year timepoint, a total of 3 events had been reported, no subjects were censored, and 49 subjects remained at risk.

Long-term Effects of Dasatinib on Growth and Development and Bone Metabolism

Z-scores decreased over time, suggesting that growth is affected in pediatric subjects with newly diagnosed Ph+ ALL following the treatment strategy in this study. The majority of the data were collected while on treatment, and therefore, data are not mature to assess longer term effects of treatment. Follow-up in subjects for the measurement of growth-related aspects of dasatinib in combination with chemotherapy continues.

Mutation Analysis

In All Treated Subjects who progressed or relapsed, 14/20 (70.0%) had mutation data at baseline and at the time of progression/relapse; of these subjects, 1 (7.1%) subject was reported with a mutation at baseline and 2 (14.3%) subjects were reported with a mutation at progression/relapse. One subject with a Q252H mutation identified at baseline developed a dasatinib-resistant T315I mutation on study, and one other subject developed a previously-uncharacterized mutation.

Overall Efficacy Conclusion

As concluded by the MAH, it can be endorsed that the efficacy of dasatinib in preventing relapse of Ph+ ALL during study treatment was shown. Only 2 subjects (both Cohorts, any Risk) showed progression during study therapy, one in bone marrow and one in CNS, and one additional subject developed secondary AML (possibly related to etoposide).The 3-year EFS rate was 79.6% in the Efficacy Sample (80.8% in the Pediatric Efficacy Sample), with a lower limit of 95% CI of 70.9% (71.8% in the pediatric subjects). Most subjects with disease relapse prior to 3 years had electively discontinued for BMT (6/18) or after completion of therapy (3 subjects). Of 44 subjects without elective transplant, 9 relapsed after 3 years (20.5%, including 1 who discontinued study treatment at Maintenance 1), but observation is continuing.

Minimal residual disease assessments, although limited by study size, support the efficacy of dasatinib. At the end of induction, only 41.4% of subjects (combined Cohorts 1 and 2, Any Risk, Efficacy Sample) (39.2% in the Pediatric Efficacy Sample) were MRD-positive compared with 70.8% in AALL0031. This reduction in MRD-positive rate may be attributed to addition of continuous dasatinib in weeks 3-4 of induction therapy. At the end of consolidation, only 10.5% of subjects were MRD-positive (9.6% in the pediatric subjects); this reduction in MRD-positive rate, although not statistically significant compared with the hypothesized 16% rate, is consistent with the higher potency of dasatinib compared with imatinib.

Safety results

Overview of Safety

A summary of safety findings (deaths, serious adverse events [SAEs], AEs leading to discontinuation, AEs, and AEs of special interest) is provided in this section for All Treated Subjects. Refer to the CA180204 CSR for safety findings in All Pediatric Treated subjects.

Two subjects were reported with dose-limiting toxicities (DLTs) during the safety phase. In one subject, the DLT was due to severe myelosuppression during Intensification Block 1, and was one of the events leading to the modification of the chemotherapy backbone (Amendment 2). In the second subject, Grade 4 sensory neuropathy was reported during Consolidation Block 1. A third subject developed prolonged Grade 3 leukoencephalopathy (per study Principal Investigator communication; also see narrative for subject CA180204-298-791948) during Intensification Block 2 after receiving high-dose [HD] methotrexate [MTX]. This and additional subjects with neurotoxicity led to Amendment 5 whereby subjects on study at that time subsequently received a single dose of intrathecal (IT) MTX (age-based dosing) rather than triple intrathecal therapy (ITT) on Day 29 of Induction, and the scheduled dose of ITT on Day 1 of Consolidation was eliminated.

Disposition and Exposure

A total of 34 (54.8%) subjects completed study treatment. The primary reasons for discontinuation of study treatment are provided in Table 4.1-1. The most common reason in both cohorts for not completing study treatment was bone marrow transplant (BMT; N = 11, 27.5% in Cohort 1; N = 7, 31.8% in Cohort 2). Of these 18 subjects, 5 were also reported as enrolled in another COG study. Only 2 subjects were reported to have disease progression during the protocol treatment.

A total of 18 (29.0%) subjects did not continue in the study. Reasons for not continuing in the study included: lost to follow-up, enrollment onto another COG study with therapeutic intent (for BMT or following relapse), death, and the special reason for 1 subject considered ineligible after having started treatment.

The median duration of dasatinib therapy from first through last dasatinib dose date was 30.9 months (Table 4.1-2). The expected number of months of actual dasatinib treatment was 16.1 (70 weeks) in Cohort 1 (discontinuous dosing) and 29.4 (128 weeks) in Cohort 2 (continuous dosing). The recorded median number of months of actual dasatinib treatment was 15.0 in Cohort 1 and 26.2 in Cohort 2.

A delay >14 days were reported in only 14 of 770 treatment blocks in 62 treated subjects.

Table 4.1-1: Subject Status Summary - All Enrolled Subjects

	Cohort 1	Cohort 2	Total
ENROLLED	41	22	63
TREATED (% OF ENROLLED)	40 (97.6)	22 (100.0)	62 (98.4)
NOT TREATED (% OF ENROLLED)	1 (2.4)	0	1 (1.6)
PHYSICIAN DETERMINES IT IS IN PATIENT'S BEST INTEREST	1 (2.4)	0	1 (1.6)
SUBJECTS COMPLETING STUDY THERAPY (%)	22 (55.0)	12 (54.5)	34 (54.8)
SUBJECTS NOT COMPLETING STUDY THERAPY (%)	18 (45.0)	10 (45.5)	28 (45.2)
REASON FOR NOT COMPLETING STUDY THERAPY (%)			
PHYSICIAN DETERMINES IT IS IN PATIENT'S BEST INTEREST	4 (10.0)	1 (4.5)	5 (8.1)
DEVELOPMENT OF A SECOND MALIGNANT NEOPLASM	0	1 (4.5)	1 (1.6)
BONE MARROW TRANSPLANT THERAPY	11 (27.5)	7 (31.8)	18 (29.0)
ADVERSE EVENT/SIDE EFFECTS/COMPLICATIONS(UNACCEPTABLE TOXICITY OR OTHER COMPLICATIONS)	1 (2.5)	0	1 (1.6)
DISEASE PROGRESSION OR RELAPSE DURING ACTIVE TREATMENT	1 (2.5)	1 (4.5)	2 (3.2)
NO REASON REPORTED - SUBJECT INELIGIBLE (*)	1 (2.5)	0	1 (1.6)
SUBJECTS CONTINUING IN THE STUDY (%)	29 (72.5)	15 (68.2)	44 (71.0)
SUBJECTS NOT CONTINUING IN THE STUDY (%)	11 (27.5)	7 (31.8)	18 (29.0)
REASON FOR NOT CONTINUING IN THE STUDY (%)			
PATIENT CONFIRMED LOST TO FOLLOW-UP	0	1 (4.5)	1 (1.6)
ENROLLMENT ONTO ANOTHER COG STUDY WITH TUMOR THERAPEUTIC INTENT	5 (12.5)	1 (4.5)	6 (9.7)
DEATH	4 (10.0)	4 (18.2)	8 (12.9)
NOT ELIGIBLE	2 (5.0)	1 (4.5)	3 (4.8)
OFF TREATMENT PERIOD (%)			
INDUCTION	0	0	0
CONSOLIDATION BLOCK 1	2 (5.0)	1 (4.5)	3 (4.8)
CONSOLIDATION BLOCK 2	8 (20.0)	5 (22.7)	13 (21.0)
RE-INDUCTION BLOCK 1	3 (7.5)	1 (4.5)	4 (6.5)
INTENSIFICATION BLOCK 1	1 (2.5)	1 (4.5)	2 (3.2)
RE-INDUCTION BLOCK 2	0	0	0
INTENSIFICATION BLOCK 2	2 (5.0)	0	2 (3.2)
MAINTENANCE CYCLE 1-4	2 (5.0)	1 (4.5)	3 (4.8)
MAINTENANCE CYCLE 5	0	0	0
MAINTENANCE CYCLE 6-12	22 (55.0)	13 (59.1)	35 (56.5)

Percentages are based on subjects treated, except where indicated otherwise.
Of the 18 subjects who discontinued study therapy to receive transplant, 5 were also reported as 'ENROLLED ONTO ANOTHER COG STUDY'.
(*) In total 3 treated subjects were found not eligible; 2 have off-treatment reason 'PHYSICIAN DETERMINES IT IS IN PATIENT'S BEST INTEREST'.
Program Source: /projects/bms214853/stats/primary/prog/tables/rt-ds.sas 05AUG2015:00:52:30

Table 4.1-2: Extent of Dasatinib Exposure Summary - Treated Subjects

	Cohort 1 N = 40	Cohort 2 N = 22	Total N = 62
DURATION OF THERAPY (MONTHS)			
MEDIAN	30.932	30.357	30.883
MIN, MAX	1.08, 34.96	1.41, 33.02	1.08, 34.96
N SUBJECTS (%) WITH <= 3	12 (30.0)	5 (22.7)	17 (27.4)
N SUBJECTS (%) WITH > 3 - 6	2 (5.0)	3 (13.6)	5 (8.1)
N SUBJECTS (%) WITH > 6 - 12	4 (10.0)	0	4 (6.5)
N SUBJECTS (%) WITH > 12 - 24	0	2 (9.1)	2 (3.2)
N SUBJECTS (%) WITH > 24 - 36	22 (55.0)	12 (54.5)	34 (54.8)
NUMBER OF DASATINIB DOSE DAYS (MONTHS)			
MEDIAN	14.965	26.168	15.179
MIN, MAX	0.69, 16.23	0.95, 31.77	0.69, 31.77
N SUBJECTS (%) WITH <= 3	14 (35.0)	6 (27.3)	20 (32.3)
N SUBJECTS (%) WITH > 3 - 6	4 (10.0)	2 (9.1)	6 (9.7)
N SUBJECTS (%) WITH > 6 - 12	0	0	0
N SUBJECTS (%) WITH > 12 - 24	22 (55.0)	2 (9.1)	24 (38.7)
N SUBJECTS (%) WITH > 24 - 36	0	12 (54.5)	12 (19.4)
AVERAGE DAILY DOSE (MG/M2/DAY)			
MEDIAN	30.473	53.367	39.642
MIN, MAX	22.07, 46.66	41.99, 76.12	22.07, 76.12
ADJUSTED AVERAGE DAILY DOSE (MG/M2/DAY)			
MEDIAN	60.594	59.974	60.517
MIN, MAX	50.00, 66.84	52.59, 92.13	50.00, 92.13
RELATIVE DOSE INTENSITY (%)			
N SUBJECTS (%) WITH 0 - 90	40 (100.0)	11 (50.0)	51 (82.3)
N SUBJECTS (%) WITH > 90 - 100	0	10 (45.5)	10 (16.1)
N SUBJECTS (%) WITH > 100 - 110	0	0	0
N SUBJECTS (%) WITH > 110	0	1 (4.5)	1 (1.6)
ADJUSTED RELATIVE DOSE INTENSITY (%)			
N SUBJECTS (%) WITH 0 - 90	1 (2.5)	1 (4.5)	2 (3.2)
N SUBJECTS (%) WITH > 90 - 100	13 (32.5)	10 (45.5)	23 (37.1)
N SUBJECTS (%) WITH > 100 - 110	25 (62.5)	10 (45.5)	35 (56.5)
N SUBJECTS (%) WITH > 110	1 (2.5)	1 (4.5)	2 (3.2)

Duration of therapy is the duration from the first through the last dasatinib dose date.
The average daily dose and the relative dose intensity are based on the duration of therapy.
The adjusted average daily dose and the adjusted relative dose intensity are based on the number of dasatinib dose days.
Relative dose intensity (%) is average dasatinib daily dose relative to 60 mg/m2 QD dasatinib.
Program Source: /projects/bms214853/stats/primary/prog/tables/rt-ex-all.sas 05AUG2015:00:53:59

Deaths

A total of 8 (12.9%) deaths were reported with 4 deaths in each cohort (refer to Table 7.2-1 of the CA180204 CSR). None of the deaths was reported within 30 days of the last dose of treatment, and

none was related to dasatinib treatment. Overall, 3 deaths were due to disease progression, and the remaining 5 were due to 'other cause' (cardiac failure, acute critical upper airway obstruction, MLL-rearranged therapy-related acute myeloid leukemia, injuries resulting from being hit by a school bus, infection due to complication of graft vs host disease).

Serious Adverse Events

The source for capturing SAEs reported during this study was Adverse Event Expedited Reporting System (AdEERS) forms. Events assigned as the 'primary reason' for SAEs are listed in Table 4.3-1. Some inconsistencies were noted between the AdEERS forms and COG AE database. Because AdEERS are submitted rapidly and may not have been revised based on subsequent information, the COG AE database was considered to be the definitive source for AE information including dates, severity, and relatedness. These inconsistencies were minor with no impact on overall safety results.

A total of 29 (46.8%) subjects were reported with SAEs, regardless of relationship to dasatinib (Cohort 1, N = 19/40 [47.5%]; Cohort 2, N = 10/22 [45.5%]) (refer to Table 7.3-1 of the CA180204 CSR). Drug-related SAEs were reported in 14 (35.0%) subjects in Cohort 1 and in 7 (31.8%) subjects in Cohort 2. Most drug-related SAEs were Grade 3/4. None led to study discontinuation.

Table 4.3-1 provides a summary of SAEs, regardless of relationship to dasatinib (All Treated Subjects).

Table 4.3-1: Summary of SAEs by CTCAE Category, Regardless of Relationship to Dasatinib; All Treated Subjects

		Number (%) Subjects		
CTCAE Category	SAE	Cohort 1 N = 40	Cohort 2 N = 22	Total N = 62
Blood and Lymphatic System Disorders				
	Febrile neutropenia	0	1 (4.5)	1 (1.6)
Cardiac				
	Hypotension	1 (2.5)	0	1 (1.6)
	Left Ventricular Systolic Dysfunction	0	1 (4.5)	1 (1.6)
	QTc Prolongation	1 (2.5)	0	1 (1.6)
Dermatology/Skin				
	Rash (Hand-foot skin reaction)	1 (2.5)	0	1 (1.6)
Gastrointestinal				
	Colitis	2 (5.0)	2 (9.1)	4 (6.5)
	Dehydration	1 (2.5)	0	1 (1.6)
	Diarrhea	1 (2.5)	0	1 (1.6)
	Nausea	0	1 (4.5)	1 (1.6)
General Disorders and Administration Site Conditions				
	Infusion related reaction	0	1 (4.5)	1 (1.6)
Hemorrhage, Bleeding				
	Abdominal Hemorrhage	1 (2.5)	0	1 (1.6)
Immune System Disorder				
	Allergic reaction	1 (2.5)	1 (4.5)	2 (3.2)
Infections and Infestations				
	Cellulitis	1 (2.5)	0	1 (1.6)
	Colitis, infectious	1 (2.5)	0	1 (1.6)
	Febrile neutropenia	2 (5.0)	0	2 (3.2)
	Neutrophil decreased	2 (5.0)	0	2 (3.2)
	Periorbital infection	1 (2.5)	0	1 (1.6)
	Upper airway infection	1 (2.5)	0	1 (1.6)
	Sepsis	1 (2.5)	0	1 (1.6)
Investigations				
	Blood bilirubin increased	1 (2.5)	0	1 (1.6)
	Creatinine increased	0	1 (4.5)	1 (1.6)
Lymphatics				
	Edema limb	0	1 (4.5)	1 (1.6)

Table 4.3-1: Summary of SAEs by CTCAE Category, Regardless of Relationship to Dasatinib; All Treated Subjects

CTCAE Category	SAE	Number (%) Subjects Cohort 1 N = 40	Cohort 2 N = 22	Total N = 62
Metabolic, Laboratory				
	Albumin - serum low	1 (2.5)	1 (4.5)	2 (3.2)
	Hypokalemia	0	2 (9.1)	2 (3.2)
	Hyponatremia	0	1 (4.5)	1 (1.6)
Muscloskeletal and Connective Tissue Disorders				
	Back Pain	0	1 (4.5)	1 (1.6)
Nervous System Disorder				
	Ifosfamide neurotoxicity	1 (2.5)	0	1 (1.6)
	Mood alteration - agitation	1 (2.5)	0	1 (1.6)
	Neurology - Motor	1 (2.5)	1 (4.5)	2 (3.2)
	Neurology - Sensory	0	1 (4.5)	1 (1.6)
	Personality/Behavioral	1 (2.5)	0	1 (1.6)
	Seizure	2 (5.0)	0	2 (3.2)
Pain				
	Headache	1 (2.5)	0	1 (1.6)
Pulmonary, Upper Respiratory				
	Dyspnea	0	1 (4.5)	1 (1.6)
	Hypoxia	1 (2.5)	0	1 (1.6)
Renal/Genitourinary				
	Renal Dysfunction	1 (2.5)	0	1 (1.6)
Vascular				
	Hypertension	1 (2.5)	0	1 (1.6)
	Superior vena cava syndrome	1 (2.5)	0	1 (1.6)
	Thombosis/thrombis/embolism	2 (5.0)	0	2 (3.2)

Source: AdEERS Forms

Discontinuations Due to Adverse Events

On-treatment toxicities or complications leading to discontinuation were reported in 2 subjects:**Error! Bookmark not defined.**

- CA204-78-790366 (Cohort 1, age 4 years): The last dose of study treatment was on 19-Jul-2009 (during re-induction). At this time, the subject was reported with Grade 4 laboratory abnormalities (WBC decreased, platelet count decreased, neutrophil count decreased). These AEs were considered not likely related to dasatinib. The subject was on study for 3.84 months. Information received from the investigator after database lock indicated that this subject was discontinued from the study due to persistent QTc prolonged, despite withdrawal of other potentially-contributing agents.
- CA204-298-791948 (Cohort 1, age 12 year): The last dose of study treatment was on 8-May-2010 (during intensification 2). At this time, the subject was reported with Grade 3 sepsis and Grade 4 febrile neutropenia. These AEs were considered not likely related to dasatinib. The subject was on study for 11.93 months. Information received from the investigator after database lock indicated that this subject was discontinued from the study due to MTX-related leukoencephalopathy.

Overall Adverse Events

Most subjects reported on-study AEs (any grade, regardless of relationship to treatment): Cohort 1, 39/40 (97.5%); Cohort 2, 21/22 (95.5%); All Treated, 60/62 (96.8%).**Error! Bookmark not defined.** Most subjects reported Grade 3/4 AEs: 37/40 (92.5%) subjects in Cohort 1, 21/22 (95.4%) subjects in Cohort 2, and 58/62 (93.5%) All Treated subjects.

The majority of subjects had at least 1 AE assessed by the investigator as related to dasatinib: Cohort 1, 32/40 (80.0%); Cohort 2, 20/22 (90.9%); All Treated, 52/62 (83.9%) (Table 4.5-1; Table 4.5-2). However, it is considered highly likely that the reported relationship was to the regimen as a whole, as these AEs are expected with intensive multi-agent chemotherapy. The most common drug-related AEs (defined as frequency ≥ 10% by cohort and overall were:

- Cohort 1: febrile neutropenia (52.5%), alanine aminotranferase (ALT) increased (45.0%), neutrophil count decreased (40.0%), aspartate aminotransferase (AST) increased (30.0%), platelet count decreased and sepsis (both 27.5%), WBC decreased and anemia (both 20.0%), hypokalemia (15.0%), decreased appetite and hypophosphatemia (12.5%), and diarrhea, stomatitis, skin infection, hypoalbuminemia, and peripheral sensory neuropathy (all 10.0%) (Table 4.5-1).
- Cohort 2: ALT increased (54.5%), neutrophil count decreased (50.0%), febrile neutropenia (45.5%), platelet count decreased (36.4%), nausea, vomiting, and hypokalemia (all 22.7%), anemia (18.2%), and AST increased, sepsis, and hyponatremia (all 13.6%) (Table 4.5-1).
- All Treated: febrile neutropenia (50.0%), ALT increased (48.4%), neutrophil count decreased (43.5%), platelet count decreased (30.6%), AST increased (24.2%), sepsis (22.6%), anemia (19.4%), hypokalemia (17.7%), WBC decreased (16.1%), and decreased appetite and nausea (both 11.3%) (Table 4.5-2).

Table 4.5-1: On-treatment Dasatinib-related AEs, Worst CTC Grade - Frequencies Equal or Higher Than 5%; By Cohort (All Treated Subjects)

Cohort 1, N = 40

System Organ Class (%) Preferred Term (%)	I	II	III	IV	V	NG(1)	Total
TOTAL SUBJECTS WITH AN EVENT (2)	1 (2.5)	0	11 (27.5)	20 (50.0)	0	0	32 (80.0)
INVESTIGATIONS	0	1 (2.5)	6 (15.0)	19 (47.5)	0	0	26 (65.0)
ALANINE AMINOTRANSFERASE INCREASED	0	1 (2.5)	13 (32.5)	4 (10.0)	0	0	18 (45.0)
NEUTROPHIL COUNT DECREASED	0	0	0	16 (40.0)	0	0	16 (40.0)
ASPARTATE AMINOTRANSFERASE INCREASED	0	1 (2.5)	10 (25.0)	1 (2.5)	0	0	12 (30.0)
PLATELET COUNT DECREASED	0	0	1 (2.5)	10 (25.0)	0	0	11 (27.5)
WHITE BLOOD CELL COUNT DECREASED	0	0	0	8 (20.0)	0	0	8 (20.0)
BLOOD BILIRUBIN INCREASED	0	1 (2.5)	0	1 (2.5)	0	0	2 (5.0)
BLOOD CREATININE INCREASED	0	1 (2.5)	1 (2.5)	0	0	0	2 (5.0)
ELECTROCARDIOGRAM QT PROLONGED	0	1 (2.5)	0	1 (2.5)	0	0	2 (5.0)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	1 (2.5)	0	1 (2.5)	0	0	0	2 (5.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	19 (47.5)	3 (7.5)	0	0	22 (55.0)
FEBRILE NEUTROPENIA	0	0	19 (47.5)	2 (5.0)	0	0	21 (52.5)
ANAEMIA	0	0	7 (17.5)	1 (2.5)	0	0	8 (20.0)
INFECTIONS AND INFESTATIONS	0	0	17 (42.5)	2 (5.0)	0	0	19 (47.5)
SEPSIS	0	0	9 (22.5)	2 (5.0)	0	0	11 (27.5)
SKIN INFECTION	0	0	3 (7.5)	1 (2.5)	0	0	4 (10.0)
ENTEROCOLITIS INFECTIOUS	0	0	3 (7.5)	0	0	0	3 (7.5)
NEUTROPENIC INFECTION	0	0	3 (7.5)	0	0	0	3 (7.5)
BRONCHITIS	0	0	2 (5.0)	0	0	0	2 (5.0)
SINUSITIS	0	0	2 (5.0)	0	0	0	2 (5.0)
UPPER RESPIRATORY TRACT INFECTION	0	0	2 (5.0)	0	0	0	2 (5.0)
METABOLISM AND NUTRITION DISORDERS	0	3 (7.5)	10 (25.0)	3 (7.5)	0	0	16 (40.0)
HYPOKALAEMIA	0	1 (2.5)	4 (10.0)	1 (2.5)	0	0	6 (15.0)
DECREASED APPETITE	0	1 (2.5)	4 (10.0)	0	0	0	5 (12.5)
HYPOPHOSPHATAEMIA	0	1 (2.5)	4 (10.0)	0	0	0	5 (12.5)
HYPOALBUMINAEMIA	0	2 (5.0)	2 (5.0)	0	0	0	4 (10.0)
HYPOCALCAEMIA	0	0	2 (5.0)	1 (2.5)	0	0	3 (7.5)
HYPONATRAEMIA	0	0	3 (7.5)	0	0	0	3 (7.5)
DEHYDRATION	0	0	2 (5.0)	0	0	0	2 (5.0)
HYPERGLYCAEMIA	0	0	0	2 (5.0)	0	0	2 (5.0)
GASTROINTESTINAL DISORDERS	2 (5.0)	2 (5.0)	9 (22.5)	0	0	0	13 (32.5)
DIARRHOEA	0	0	4 (10.0)	0	0	0	4 (10.0)
STOMATITIS	1 (2.5)	1 (2.5)	2 (5.0)	0	0	0	4 (10.0)
NEUTROPENIC COLITIS	0	0	3 (7.5)	0	0	0	3 (7.5)
COLITIS	0	0	2 (5.0)	0	0	0	2 (5.0)
NAUSEA	1 (2.5)	0	1 (2.5)	0	0	0	2 (5.0)
NERVOUS SYSTEM DISORDERS	3 (7.5)	1 (2.5)	3 (7.5)	0	0	0	7 (17.5)
PERIPHERAL SENSORY NEUROPATHY	2 (5.0)	1 (2.5)	1 (2.5)	0	0	0	4 (10.0)
HEADACHE	0	0	3 (7.5)	0	0	0	3 (7.5)
VASCULAR DISORDERS	0	1 (2.5)	5 (12.5)	0	0	0	6 (15.0)
EMBOLISM	0	0	2 (5.0)	0	0	0	2 (5.0)
HYPOTENSION	0	1 (2.5)	1 (2.5)	0	0	0	2 (5.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	3 (7.5)	2 (5.0)	0	0	0	5 (12.5)
DERMATITIS ACNEIFORM	0	2 (5.0)	0	0	0	0	2 (5.0)
RASH MACULO-PAPULAR	1 (2.5)	1 (2.5)	0	0	0	0	2 (5.0)

Cohort 2, N = 22

System Organ Class (%) Preferred Term (%)	I	II	III	IV	V	NG(1)	Total
TOTAL SUBJECTS WITH AN EVENT (2)	0	1 (4.5)	4 (18.2)	15 (68.2)	0	0	20 (90.9)
INVESTIGATIONS	0	0	3 (13.6)	15 (68.2)	0	0	18 (81.8)
ALANINE AMINOTRANSFERASE INCREASED	0	0	9 (40.9)	3 (13.6)	0	0	12 (54.5)
NEUTROPHIL COUNT DECREASED	0	0	0	11 (50.0)	0	0	11 (50.0)
PLATELET COUNT DECREASED	0	0	1 (4.5)	7 (31.8)	0	0	8 (36.4)
ASPARTATE AMINOTRANSFERASE INCREASED	0	1 (4.5)	2 (9.1)	0	0	0	3 (13.6)
WHITE BLOOD CELL COUNT DECREASED	0	0	0	2 (9.1)	0	0	2 (9.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	9 (40.9)	2 (9.1)	0	0	11 (50.0)
FEBRILE NEUTROPENIA	0	0	9 (40.9)	1 (4.5)	0	0	10 (45.5)
ANAEMIA	0	0	2 (9.1)	2 (9.1)	0	0	4 (18.2)
GASTROINTESTINAL DISORDERS	0	2 (9.1)	4 (18.2)	2 (9.1)	0	0	8 (36.4)
NAUSEA	0	1 (4.5)	3 (13.6)	1 (4.5)	0	0	5 (22.7)
VOMITING	0	2 (9.1)	3 (13.6)	0	0	0	5 (22.7)
COLITIS	0	0	1 (4.5)	1 (4.5)	0	0	2 (9.1)
DIARRHOEA	0	0	2 (9.1)	0	0	0	2 (9.1)
GASTRITIS	0	1 (4.5)	1 (4.5)	0	0	0	2 (9.1)
STOMATITIS	0	0	2 (9.1)	0	0	0	2 (9.1)
INFECTIONS AND INFESTATIONS	0	0	6 (27.3)	1 (4.5)	0	0	7 (31.8)
SEPSIS	0	0	3 (13.6)	0	0	0	3 (13.6)
CLOSTRIDIUM DIFFICILE INFECTION	0	0	2 (9.1)	0	0	0	2 (9.1)
OTITIS MEDIA	0	0	1 (4.5)	1 (4.5)	0	0	2 (9.1)
PNEUMONIA	0	0	2 (9.1)	0	0	0	2 (9.1)
METABOLISM AND NUTRITION DISORDERS	0	1 (4.5)	4 (18.2)	2 (9.1)	0	0	7 (31.8)
HYPOKALAEMIA	0	0	3 (13.6)	2 (9.1)	0	0	5 (22.7)
HYPONATRAEMIA	0	0	3 (13.6)	0	0	0	3 (13.6)
DECREASED APPETITE	0	1 (4.5)	1 (4.5)	0	0	0	2 (9.1)
DEHYDRATION	0	0	2 (9.1)	0	0	0	2 (9.1)
NERVOUS SYSTEM DISORDERS	0	2 (9.1)	2 (9.1)	1 (4.5)	0	0	5 (22.7)
HEADACHE	0	0	2 (9.1)	0	0	0	2 (9.1)
PERIPHERAL MOTOR NEUROPATHY	1 (4.5)	0	1 (4.5)	0	0	0	2 (9.1)
PERIPHERAL SENSORY NEUROPATHY	0	1 (4.5)	0	1 (4.5)	0	0	2 (9.1)
VASCULAR DISORDERS	0	0	2 (9.1)	1 (4.5)	0	0	3 (13.6)
HYPOTENSION	0	0	1 (4.5)	1 (4.5)	0	0	2 (9.1)

(1) Toxicity reported but not graded.
(2) Subjects may have more than 1 event within a System Organ Class.
MedDRA Version: 17.1

Adverse Events of Special Interest

Safety issues of special interest in the dasatinib program were examined either because of their association with dasatinib in the currently approved indications, because they are recognized events in other agents within this drug class, or because safety data from non-clinical and clinical studies warranted careful evaluation.

Adverse events of special interest include fluid retention (including the subcategories of superficial edema, pleural effusion, and other fluid-related endpoints [pericardial effusion, generalized edema, CHF/cardiac dysfunction, pulmonary edema, pulmonary hypertension]), pulmonary arterial hypertension (PAH), hemorrhage (gastrointestinal [GI] bleeding, CNS bleeding, and other hemorrhage), selected cardiac events, arterial ischemic events, diarrhea, nausea/vomiting, fatigue, myalgias/arthralgias, and rash. These events are described in this section.

Dasatinib-related fluid retention-related AEs were infrequent in both cohorts (Table 4.6-1; Table 4.6-2). Severe events (Grade 3/4) reported included one subject in Cohort 1 with generalized edema and one subject in Cohort 2 with superficial edema. No cases of dasatinib-related pleural effusion, pericardial effusion, pulmonary hypertension, or PAH were reported.

Drug-related hemorrhage was reported in 3 subjects, reported as an SAE (GI bleeding) in 1 subject (CA204-117-801809), but all were considered severe: Cohort 1 had 2 subjects, one with GI bleeding and 1 with “other hemorrhage”; Cohort 2 had 1 subject with “other hemorrhage” (Table 4.6-1). Other AEs of interest that had an overall frequency of ≥5% in All Treated subjects were nausea/vomiting (9/62, 14.5%), diarrhea (6/62, 9.7%), and rash (4/62, 6.5%) (Table 4.6-2). Most were severe.

Table 4.6-1: Dasatinib-related Adverse Events of Special Interest, Any vs Severe; By Cohort (All Treated Subjects)

Cohort 1, N = 40

	Number of Subjects (%)		
AE of Special Interest	Any Grade	Severe (3-4)	Grade 5
FLUID RETENTION	1 (2.5)	1 (2.5)	0
SUPERFICIAL EDEMA	0	0	0
PLEURAL EFFUSION	0	0	0
OTHER FLUID RELATED	1 (2.5)	1 (2.5)	0
GENERALIZED EDEMA	1 (2.5)	1 (2.5)	0
ASCITES	0	0	0
PERICARDIAL EFFUSION	0	0	0
CONGESTIVE HEART FAILURE/CARDIAC DYSFUNCTION	0	0	0
PULMONARY EDEMA	0	0	0
PULMONARY HYPERTENSION	0	0	0
RESPIRATORY DISORDERS	1 (2.5)	0	0
CHEST PAIN	0	0	0
NON-PRODUCTIVE COUGH	0	0	0
SHORTNESS OF BREATH	1 (2.5)	0	0
CARDIAC DISORDERS	1 (2.5)	0	0
PULMONARY ARTERIAL HYPERTENSION	0	0	0
DIARRHEA	4 (10.0)	4 (10.0)	0
NAUSEA/VOMITTING	3 (7.5)	2 (5.0)	0
FATIGUE	0	0	0
MYALGIAS/ARTHRALGIAS	1 (2.5)	0	0
RASH	4 (10.0)	1 (2.5)	0
HEMORRHAGE	2 (5.0)	2 (5.0)	0
GI BLEEDING	1 (2.5)	1 (2.5)	0
CNS BLEEDING	0	0	0
OTHER HEMORRHAGE	1 (2.5)	1 (2.5)	0

Cohort 2, N = 22

	Number of Subjects (%)		
AE of Special Interest	Any Grade	Severe (3-4)	Grade 5
FLUID RETENTION	2 (9.1)	1 (4.5)	0
SUPERFICIAL EDEMA	1 (4.5)	1 (4.5)	0
PLEURAL EFFUSION	0	0	0
OTHER FLUID RELATED	1 (4.5)	0	0
GENERALIZED EDEMA	0	0	0
ASCITES	0	0	0
PERICARDIAL EFFUSION	0	0	0
CONGESTIVE HEART FAILURE/CARDIAC DYSFUNCTION	1 (4.5)	0	0
PULMONARY EDEMA	0	0	0
PULMONARY HYPERTENSION	0	0	0
RESPIRATORY DISORDERS	1 (4.5)	1 (4.5)	0
CHEST PAIN	0	0	0
NON-PRODUCTIVE COUGH	0	0	0
SHORTNESS OF BREATH	1 (4.5)	1 (4.5)	0
CARDIAC DISORDERS	0	0	0
PULMONARY ARTERIAL HYPERTENSION	0	0	0
DIARRHEA	2 (9.1)	2 (9.1)	0
NAUSEA/VOMITTING	6 (27.3)	4 (18.2)	0
FATIGUE	0	0	0
MYALGIAS/ARTHRALGIAS	0	0	0
RASH	0	0	0
HEMORRHAGE	1 (4.5)	1 (4.5)	0
GI BLEEDING	0	0	0
CNS BLEEDING	0	0	0
OTHER HEMORRHAGE	1 (4.5)	1 (4.5)	0

Table 4.6-2: Dasatinib-related Adverse Events of Special Interest, Any vs Severe; All Treated Subjects

All Treated Subjects, N = 62

AE of Special Interest	Number of Subjects (%)		
	Any Grade	Severe (3-4)	Grade 5
FLUID RETENTION	3 (4.8)	2 (3.2)	0
SUPERFICIAL EDEMA	1 (1.6)	1 (1.6)	0
PLEURAL EFFUSION	0	0	0
OTHER FLUID RELATED	2 (3.2)	1 (1.6)	0
GENERALIZED EDEMA	1 (1.6)	1 (1.6)	0
ASCITES	0	0	0
PERICARDIAL EFFUSION	0	0	0
CONGESTIVE HEART FAILURE/CARDIAC DYSFUNCTION	1 (1.6)	0	0
PULMONARY EDEMA	0	0	0
PULMONARY HYPERTENSION	0	0	0
RESPIRATORY DISORDERS	2 (3.2)	1 (1.6)	0
CHEST PAIN	0	0	0
NON-PRODUCTIVE COUGH	0	0	0
SHORTNESS OF BREATH	2 (3.2)	1 (1.6)	0
CARDIAC DISORDERS	1 (1.6)	0	0
PULMONARY ARTERIAL HYPERTENSION	0	0	0
DIARRHEA	6 (9.7)	6 (9.7)	0
NAUSEA/VOMITTING	9 (14.5)	6 (9.7)	0
FATIGUE	0	0	0
MYALGIAS/ARTHRALGIAS	1 (1.6)	0	0
RASH	4 (6.5)	1 (1.6)	0
HEMORRHAGE	3 (4.8)	3 (4.8)	0
GI BLEEDING	1 (1.6)	1 (1.6)	0
CNS BLEEDING	0	0	0
OTHER HEMORRHAGE	2 (3.2)	2 (3.2)	0

Overall Safety Conclusions

As concluded by the MAH, it can be endorsed that dasatinib at 60 mg/m^2/day on the continuous schedule was well tolerated in combination with intensive multi-agent chemotherapy. Dasatinib discontinuous and continuous dosing schedules were equally tolerable. The planned dose of dasatinib was administered in almost all subjects.

Of the 8 deaths reported, none was reported within 30 days of the last dose of treatment, and none was related to dasatinib treatment. Toxicities or complications leading to discontinuation were reported in 2 subjects, and were not considered related to dasatinib treatment. Overall, 83.9% subjects had at least 1 AE assessed by the investigator as related to treatment, the majority of which were considered severe (Grade 3-4). Myelosuppression was common (defined as ≥□20.0%) as expected with intensive chemotherapy.

Dasatinib-related fluid retention-related AEs were infrequent in both cohorts. Severe events (Grade 3/4) reported included one subject in Cohort 1 with generalized edema and one subject in Cohort 2 with superficial edema. No cases of dasatinib-related pleural effusion, pericardial effusion, pulmonary hypertension, or PAH were reported. Drug-related hemorrhage was reported in 3 subjects (2 subjects in Cohort 1 and 1 subject in Cohort 2), reported as an SAE (GI bleeding) in 1 subject, but all were considered severe

Discussion on clinical aspects

The conclusion and discussion as provided by the MAH is fully acceptable. It is agreed that despite early termination of this study (in favor of CA180372, an international study in the same clinical setting), study CA180204 was able to achieve multiple key aims. A total of 62 subjects were treated, of whom 40 received dasatinib on the discontinuous regimen (70 weeks) and 22 received dasatinib on the continuous regimen (128 weeks).

The safety and tolerability of dasatinib were demonstrated when added to an intensive chemotherapy regimen for the treatment for Ph+ ALL in pediatric subjects. Only two subjects discontinued due to an

AE (not dasatinib-related) and the 2 DLTs (which prompted safety-related amendments) were not dasatinib-related. Discontinuation for elective BMT was the most common reason (18 subjects) for not completing protocol-defined treatment.

Disease control using dasatinib with chemotherapy was achieved, with overall 3-year EFS rate of 79.6% (80.8% in the pediatric sample), meeting the pre-defined target. Recurrence during treatment was very uncommon (2/62, 3.2%). Most relapses within 3 years were in subjects discontinued at Week 12 for allogeneic transplant; longer dasatinib exposure appears warranted in this setting.

Safety and efficacy data in this study support a favorable benefit risk profile for dasatinib on the continuous schedule in combination with intensive multi-agent chemotherapy in pediatric subjects with Ph+ ALL.

As stated by the MAH, the submitted study is part of a clinical development program and a variation application consisting of the full relevant paediatric data package is expected to be submitted during the first half of 2018.

It is considered that the data included in this submission do not at this time influence the benefit-risk balance for Sprycel and currently do not require further updates of the Sprycel Summary of Product Characteristics,

3. Rapporteur's overall conclusion and recommendation

X Fulfilled:

No regulatory action required.

4. Additional clarification requested

NA